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Molecular mechanisms in atopic eczema: insight gained from genetic studies

Running title: Molecular genetic mechanisms in eczema

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Conflict of interest statement

The author has filed a patent application (GB 1602011.7) relating to a mechanism for the gene *EMSY* in skin; she has received honoraria for invited lectures at the American Academy of Asthma, Allergy and Immunology annual meetings.

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Abstract

Atopic eczema (synonymous with atopic dermatitis and eczema) is a common heterogeneous phenotype with a wide spectrum of severity from mild transient disease to a severe chronic disorder with atopic and non-atopic co-morbidities. Eczema is a complex trait, resulting from the interaction of multiple genetic and environmental factors. Skin as an organ that can be biopsied easily provides the opportunity for detailed molecular genetic analysis. Strategies applied to the investigation of atopic eczema include candidate gene and genome-wide studies, extreme phenotypes and comparative analysis of inflammatory skin diseases. Genetic studies have identified a central role for skin barrier impairment in eczema predisposition and perpetuation; this has brought about a paradigm shift in understanding atopic disease but specific molecular targets to improve skin barrier function remain elusive. The role of Th2-mediated immune dysfunction is also central to atopic inflammation and has proved to be a powerful target for biological therapy in atopic eczema. Advances in understanding eczema pathogenesis have provided opportunities for patient stratification, primary prevention and therapy development, but there remain considerable challenges in the application of this knowledge to optimise benefit for patients with atopic eczema in the era of personalised medicine.

Key words

Atopic eczema, dermatitis, filaggrin, genome-wide, phenotype, skin barrier, therapy, transcriptome

Molecular mechanisms in atopic eczema: insight gained from genetic studies

Importance of eczema genetic studies

Atopic eczema (a diagnostic term which is synonymous with 'atopic dermatitis' and 'eczema') [1] is an itchy inflammatory skin condition associated with significant morbidity. It is a strongly heritable disease, demonstrating the importance of genetic mechanisms in pathogenesis, but its rapid rise in prevalence over recent decades worldwide has also indicated the importance of environmental factors [2].

Atopic eczema is a common disease, affecting up to 25% of school-aged children (with a range from 0.2% to 24.6% worldwide) [3,4] and up to 10% of adults [5]. It characteristically presents in childhood and 70% of cases show onset before 5 years of age [6]. However eczema follows a chronic relapsing and remitting course with over 10% of cases persisting into adult life or recurring in adulthood [6].

Approximately 40% of patients with eczema have systemic atopic co-morbidities including asthma, allergic rhinitis and IgE-mediated food allergies [6,7] which substantially add to the burden of disease. Other co-morbidities have been suggested from epidemiological studies [8], including depression [9], attention-deficit hyperactivity disorder [10] rheumatoid arthritis and inflammatory bowel disease [11], hypertension and obesity [12,13]; however the shared risk factors and pathomechanisms are unclear.

Despite the high prevalence of eczema, the pathogenesis of this condition remains incompletely understood. Atopic eczema is a heterogeneous phenotype [14]; it results from the interplay of skin barrier impairment and immunological dysfunction, both of which are determined in part by genetic factors (**Figure 1**). Genetic studies over recent years have played a major role in transforming the understanding of atopic eczema from a disease seen as a primarily immune-mediated disorder to one

that may arise from a primary or secondary skin barrier impairment (**Figure 1**). However specific immune dysfunction (characterised by a Th2 and Th22 response) clearly also plays a significant role in the development of atopic eczema.

Strategies for investigation

Atopic eczema is a complex trait, resulting from the interaction of multiple genetic and environmental risk factors. In parallel with other complex traits, the strategies for investigating eczema risk have included the study of candidate genes and extreme phenotypes as well as genome-wide analyses and most recently exome or genome sequencing (**Figure 2**). Mouse models have provided some valuable insights; these are reviewed elsewhere [15] and this review will focus on human studies. Eczema research has the advantage of relatively easy access to normal as well as diseased tissue, which has allowed the addition of detailed gene expression studies to aid the investigation of molecular mechanisms. Finally, eczema can be compared and contrasted to the second most common inflammatory skin disease, psoriasis, for further insight into shared and opposing disease mechanisms (**Figure 2**). Each of these strategies will be considered, briefly, in turn.

Candidate gene studies

Many candidate genes have been selected for investigation in relation to eczema pathogenesis because of their theoretical role in epidermal differentiation, skin or systemic immunity [16]. Notable findings include a role for variants in the genes encoding interleukin-4 (IL-4), the IL-4 receptor and IL-13 [17,18]; these associations have been replicated in candidate gene studies and subsequently supported by

genome-wide association loci (see below). However, the strongest association and that which has been most widely replicated for a candidate gene for atopic eczema is the gene encoding filaggrin (*FLG*) [7,19,20]. This protein is expressed in the epidermal granular layer and has multiple inter-related functions contributing to skin barrier development and maintenance [21]. The functions of filaggrin include keratin filament aggregation (from which it derives its name), contribution of hygroscopic and acidic amino acids to the stratum corneum and anti-microbial effects [22]. Loss-of-function mutations in *FLG* are present in up to 10% of the general population; they cause the common monogenetic dry skin disorder ichthyosis vulgaris [23]. Ichthyosis vulgaris exhibits a semi-dominant inheritance, such that homozygous (or compound heterozygous) individuals have the full phenotype of dry scaly skin, hyperlinear palms and keratosis pilaris, whilst individuals heterozygous for *FLG* null mutations have a milder dry (xerotic) and/or ichthyotic skin phenotype [24]. The same null mutations are found in up to 40% of patients with moderate-severe atopic eczema and meta-analysis has shown the risk for eczema in an individual carrying one or more *FLG* loss-of-function mutation(s) to be increased 3-fold (odds ratio 3.12, 95% confidence interval 2.57-3.79) [20]. This illustrates a remarkably strong effect for a single gene in the context of a complex trait. The central effect of filaggrin in skin physiology has been further demonstrated by a dose-dependent effect of copy number variation within this repetitive gene sequence [25] and by the effect of atopic inflammatory cytokines which suppress filaggrin expression in the skin resulting in additional barrier impairment [26,27].

Study of extreme phenotypes

Atopic eczema itself varies from a mild, self-limiting skin disease to a severe, chronic disorder affecting the entire skin surface, with multisystem involvement and life-long morbidity. However, severe phenotypes with monogenic inheritance have also offered insight into mechanisms giving rise to atopic skin inflammation. Netherton syndrome (OMIM #256500) is an autosomal recessive condition caused by mutations in *SPINK5*, encoding a serine protease inhibitor, LEKTI. Features of Netherton syndrome include an ichthyotic (dry, scaly) and eczematous skin phenotype and markedly raised IgE. Several independent studies have shown an association between *SPINK5* variants and atopic eczema [28-30]. This indicates the importance of the protease-antiprotease balance in maintaining an optimal skin barrier function. The control of proteases by protease inhibitors is crucial in the co-ordinated differentiation and desquamation of the outer epidermis [31] and also plays an important role in the cutaneous response to allergens, many of which are, or contain proteases [32].

Another extreme phenotype of atopic skin disease is the syndrome of severe dermatitis, multiple allergies and metabolic wasting (SAM), for which the genes *DSG1* (encoding desmoglein 1) and *DSP* (encoding desmoplakin) have each been implicated [33,34]. Desmosomes are intercellular junctions which provide mechanical strength to the skin and are degraded in a controlled way during physiological desquamation [31]; they also play a key role in cell signaling [35]. The finding of mutations in *DSG1* and *DSP* causing SAM indicates the importance of desmosomal proteins in protecting against local and systemic atopic inflammation. Importantly, there are forms of more extreme skin barrier impairment which do not appear to predispose to atopic inflammation, such as epidermolysis bullosa;

furthermore, recent molecular profiling of patients with several different rare monogenic ichthyoses has suggested they may share the feature of Th17 immune activation [36]. This illustrates the complex and specific role of transcutaneous sensitization in allergic disease.

Genome-wide analyses

The first genome-wide association study (GWAS) for atopic eczema was published in 2009 representing the white European population [37]; this identified the locus on chromosome 1q21.3 (the epidermal differentiation complex which includes *FLG*) as well as a locus on 11q13.5, in an intergenic region of unknown function; subsequent GWAS analyses have replicated these findings. A meta-analysis incorporating published and unpublished data was completed in 2015 [38] which included over 15 million genetic variants in >20,000 cases and >95,000 controls from populations of European, African, Japanese and Latino ancestry, followed by replication in >250,000 eczema cases and controls. This powerful meta-analysis detected 10 additional risk loci, bringing the total number of eczema risk loci identified to date to 31. The majority of GWAS loci are in intergenic or intronic regions for which the function remains unclear, however where functions can be inferred these have largely been attributed to skin barrier development, innate and acquired immunity. The most recently identified loci have been proposed to identify genes with roles in the regulation of innate host defence and T cell function, supporting a possible role for autoimmune mechanisms in eczema pathogenesis [38,39].

Whole exome sequencing (WES), in which the coding DNA is captured and sequenced (as opposed to the genotyping of selected single nucleotide variants in

GWAS) has contributed to the diagnosis of extreme phenotypes in rare diseases (including SAM, described above [34]) and offered greater detail in the search for rare variants causing common diseases. To date only one small WES study has been reported for eczema, in which 22 Ethiopian patients with ichthyosis vulgaris and atopic eczema were sequenced, identifying possible disease-causing variants in *FLG* and related genes as well as some novel candidate genes in a rather heterogeneous pattern of risk [40]. Exome sequencing data has been reported for *FLG* and related genes [41] as well as for the HLA region [42], however larger studies will be required to begin to systemically identify rare variants contributing to atopic eczema. In addition, whole genome sequencing and painstaking functional studies will be required to fully assess the complex contribution of non-coding genetic variants, which is anticipated to be substantial [43,44].

Transcriptome analyses

The accessibility of skin tissue has allowed the detailed comparison of gene expression patterns in lesional (active eczematous skin) compared with non-lesional (uninflamed skin on a patient with eczema) and normal skin (from a non-atopic individual). Whole transcriptome analyses, using RNA sequencing techniques provide more comprehensive assessment and more detailed quantification of mRNA than previous microarray studies. Several studies have identified networks of differentially expressed genes involved in keratinocyte differentiation in the epidermis, innate and acquired immune responses as well as lipid metabolism [45-47]. Laser capture microdissection has recently been used to separate the dermal and epidermal gene expression signatures, identifying some novel immune and barrier genes [48] which require further validation.

Eczema compared and contrasted with psoriasis

The final approach recently used to investigate genetic mechanisms in eczema has been a comparison of the two most common inflammatory skin diseases: eczema and psoriasis. These diseases are usually mutually exclusive in clinical practice, but very rare cases have both eczematous and psoriatic skin lesions simultaneously.

The concept of mutually antagonistic T cells in psoriasis and eczema has been proposed, being triggered by specific antigens in each disease [49]. On a genome-wide level the two diseases show considerable overlap in risk loci, including the epidermal differentiation complex (chromosome 1q21.3), the Th2 locus control region (chromosome 5q31.1) and the major histocompatibility complex (chromosome 6p21-22). This observation has been used to perform a genome-wide comparative analysis, to investigate shared and opposing mechanisms leading to eczema or psoriasis [50]. Notably there were no shared loci with effects operating in the same direction on both diseases; instead atopic eczema and psoriasis appear to have distinct genetic mechanisms with opposing effects in pathways influencing epidermal differentiation and immune response [50].

Application of molecular genetic insights

The strong effect of *FLG* null mutations on eczema pathogenesis has identified a clinically relevant sub-group of patients with more significant atopic pathology.

Individuals with one or more loss-of-function mutations in *FLG* are at increased risk of early-onset, severe and persistent eczema [51,52]; a greater prevalence of atopic co-morbidities [7,52,53]; and higher incidence of eczema herpeticum [54], a severe and potentially life-threatening spread of herpes simplex virus within areas of

inflamed atopic skin [14]. These observations have enabled clinicians to provide clearer prognostic guidance for patients. Targeted therapeutic intervention to increase filaggrin expression has been anticipated but has not yet been developed.

The central role of skin barrier impairment in the genetic predisposition to eczema as well as its acute and chronic pathology has drawn attention to this feature as a therapeutic target. Skin barrier impairment as defined by trans-epidermal water loss (TEWL), can be measured non-invasively *in vivo* and is a feature of atopic skin even in the absence of active eczema (**Figure 1**). Furthermore, elevated TEWL is not solely explained by loss-of-function mutations in *FLG*; it is apparent as early as two days after birth and it predates the onset of eczema [55,56]. These observations have provided rationale for early intervention studies, designed to improve skin barrier function for the primary prevention of atopic eczema. Two randomised controlled studies [57,58] have each shown that daily application of emollient to the whole skin surface beginning within 3 weeks of birth can reduce the incidence of atopic eczema in high-risk infants by approximately 50%. The authors of the UK study have now embarked on a larger, more definitive study ('BEEP' ISRCTN21528841). This randomised intervention study will include 2 years' follow up to assess whether intensive emollient treatment can reduce the incidence of atopic asthma, hay fever and food allergy, in addition to preventing or delaying the onset of eczema. The study design includes, in the secondary analyses, stratification for *FLG* genotype to test the hypothesis that filaggrin haploinsufficiency (a genetically-determined reduction in filaggrin expression) affects response to emollient treatment. If this is the case, future strategies would allow higher-risk infants to be targeted for primary prevention.

The central role of Th2/Th22 inflammation in eczema pathogenesis was clear before the genetic studies supported its role and this inflammatory pathway has been at the forefront of therapeutic trials. The development of dupilumab, a fully human monoclonal antibody targeting the interleukin-4 receptor to inhibit signalling via IL-4 and IL-13 appears to be a major step forward in treatment [59]. In phase 1 trials, ~85% of patients showed 50% reduction in eczema severity score (compared with ~35% in the placebo group, $p < 0.001$) [60] and phase 2b clinical trials have shown a dose-dependent response with a rapid onset of effect (within 4 weeks) [61], emphasising the central role of IL-4 and IL-13 in atopic eczema. Studies of the efficacy of dupilumab in the paediatric population are currently on-going [62].

In contrast to dupilumab, omalizumab, a recombinant humanized monoclonal antibody that binds to the high-affinity Fc receptor of IgE, has shown limited efficacy in the treatment of atopic eczema [63]. The extent of response in different patients is rather variable and does not appear to correlate with IgE level; instead there is some evidence that a response to omalizumab is more likely in patients with disordered lipid metabolite profiles and in the absence of *FLG* mutations [64].

Most recently, a phosphodiesterase-4 (PDE-4) inhibitor, crisaborole, which can be applied topically to the skin, has shown some efficacy in phase III clinical trials [65]. However, atopic eczema continues to lag behind psoriasis in the armamentarium of biologic treatments and additional agents, targeted at other components of the inflammatory cytokine network are anticipated. Our understanding of the complex pathophysiology of eczema would suggest that a bi-pronged approach, targeting both the immune dysregulation and the skin barrier impairment may be required to optimise treatment and to gain control of established severe disease.

Opportunities and outstanding challenges

The identification of genetically determined skin barrier dysfunction in eczema pathogenesis 10 years ago [19] has brought about a paradigm shift in understanding atopic disease. This in turn has raised the exciting possibility that atopic eczema (as well as atopic asthma, allergic rhinitis and food allergy) may be treated and/or prevented by effective barrier protection and/or repair. The challenge remains to ascertain whether a simple emollient will be sufficient to bring such a therapeutic effect or whether bespoke molecular interventions are required.

GWAS has indicated many additional risk loci for eczema, but for the majority the mechanisms leading to atopic skin inflammation remain unknown and the gene-gene and gene-environment interactions are largely unexplored. Further investigation of these disease mechanisms offers the opportunity to understand not only eczema but also the substantial burden of atopic co-morbidities. Furthermore, strategic developments in drug discovery will allow the application of genetic insight to the development of novel targeted treatments [66] and in return a better understanding of genetic mechanisms will facilitate patient stratification in this heterogeneous phenotype. The ultimate aim of personalised treatment is a genuinely exciting prospect for the foreseeable future for patients affected by atopic eczema.

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Statement of author contributions

This manuscript was planned, written and illustrated by Sara J Brown.

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Figure titles and legends

Figure 1. Simplified representation of inter-related mechanisms in the pathogenesis of atopic eczema

Genetic studies have identified the role of variants predisposing to skin barrier impairment, local and systemic atopic inflammation; the penetration of allergens and irritants can lead to a cycle of acute and chronically relapsing atopic eczema.

Figure 2. Investigative strategies, insights and application of knowledge of genetic mechanisms in atopic eczema

Skin, as an organ which can be easily biopsied, offers the opportunity for detailed molecular genetic investigation; this has provided valuable insights to improve our understanding of eczema pathogenesis, leading to clinical application and a promising future for personalised medicine. Central panel shows haematoxylin and eosin stained biopsy (x100 magnification) from the neck skin of a 49 year old male patient with atopic eczema, showing histological features including hyperkeratosis, epidermal spongiosis, a reduction in keratohyaline granules and mixed inflammatory cell infiltrate. GWAS, genome-wide association analysis; WES, whole exome sequencing.